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The Evolution of Wound Healing
From Art to Science

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INTRODUCTION

Man's struggle to heal wounds is as old as history itself. As life forms evolved from single cell life to amphibian and finally mammal, the pristine ability to heal by regeneration was lost and thus repairs by inflammation and subsequent deposition of matrix protein (scar) evolved as the method of mammalian healing. This evolutionary change leading to scar (the deposition of collagen) seems to be the key to preventing regeneration. It is well known that when the point is reached on the ladder where regeneration on longer occurs, inflammation and collagen deposition are the difference. In fact, if one takes a form of life, which seems the first link between regeneration and scar formation and a collagen cross-linking inhibitor is fed to the animal, then regeneration will once again occur! If we could only bridge this gap, imagine how successful we could become in the management of diabetic wounds. Although uncertain regarding why this occurred in the evolutionary process, it is hypothesized that as mammals became sophisticated, they needed rapid healing to protect themselves from other predators and to eke out a physical survival in a very hostile environment. In early-recorded history, the Egyptians repaired wounds with primitive suture materials (such as insect claws) and used clean sheets on surgical fields to prevent "suppuration." The Greeks, led by Hippocrates, devised methods of treatment for primary wounds and chronic wounds. They used various gauze materials empirically which included wine, milk, honey, and other substances in open wounds similar to our treatment today. Today, one can assign scientific rationale to some of these ancient empirical choices. For example, the complex sugars of honey are known to suppress the growth of Gram-positive bacteria. Wine will suppress pseudomonas proliferation. Milk products may contain cytokines or serve as buffers to control wound pH. Although the ancients had no idea that pus was actually is made up of proteins and dead leukocytes, they understood that drainage of localized products of infection was a good sign (laudable pus). They understood that when signs opf inflammation could not be localized that death would inevitably follow. During the early Roman era, Celsius, unaware of the existence of bacteria, did recognize and describe the cardinal signs of clinical infection being (1) *rubor*—erythema, (2) *tumor*—swelling, (3) *dolor*—pain, and (4) *calor*—heat.

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THE ORIGINS OF SCIENTIFIC STUDYING OF THE WOUND

Even the ancients took a scientific approach to wound healing by their observations, rationale, and conclusions. However, during the Dark Ages the domination of the church over thought processes overran the free thinkers in the arts and the sciences. Regardless, each generation brought forth new tools for the scientific mind to utilize for discovery and progress in wound healing. For example, Pare, the young French surgeon in the 16th century (1510–1590) made the following observations on the battlefield, which allowed him to "think out of the box" and radically change principles of wound management. "I had not yet seen wounds made by gun shot … it is true I had read in John de Vigo that wounds made by weapons of fire for their cure commands to cauterize them with oyle of Elders scalding hot…I was willing to know first, before I applied it, how the other Chirurgions did which was to apply the sayd oyle the hottest that was possible in the wounds insomuch as I took courage to doe as they did. At last I wanted oyle, and was constrained in steed therefore, to apply a digestive of yolks of eggs, oyle of Roses, and Turpentine. In the night I could not sleep in quiet, fearing some default in not cauterizing, that I should find those to whom I had not used the burning oyle dead impoysoned; which made me rise very early to visit them, where beyond my expectation I found those to whom I had applied my digestive medicine, to feel little pain, and their wounds without inflammation or tumor, having rested reasonably well in the night: the others to whom was used the sayd burnign oyle, I found them feverish, with great pain and tumor about the edges of their wounds." Therefore, Pare concluded, "And I resolved with myself never so cruelly, to burne poore men wounded with gunshot."

In the 17th century, great minds such as John Hunter (…) interested in science, anatomy and evolution could not be suppressed. Just one of his accomplishments was the first description of angiogenesis (one of the hot buttons at the moment for diabetic healing research). Hunter hypothesized that obliteration of blood flow would impede growth. Therefore, he ligated the carotid artery of a young deer and then observed antler growth on the ligated compared with the normal side. To his surprise, antler growth was retarded for a short period of time but then growth began again until the antler reached normal size. He hypothesized that the ligature had come off the carotid. When he sacrificed the animal, he was surprised to find that the ligature was intact but there was extensive growth of new vessels in the area, which compensated for the ablated blood flow from carotid ligation. Therefore, he concluded that hypoxia had stimulated new blood vessel growth and although he did not know the factor involved, he coined the phrase angiogenesis to brand his observation. This occurred over 200 years before the seminal work of Judah Folkman. Think of the impact today on cancer and wound research and treatment. It is quite possible that the poor blood flow in diabetes is not only related to nitric oxide vascular changes but also to a lack of angiogenesis in diabetic wounds related to wound proteases, which destroy the angiogenic growth factors.

In the 18th and 19th centuries came the recognition that a factor passed from care givers to patients would kill. These observations were made by Holmes, Semmelweiss, and many others. All were rejected by the leading professors of the day. The failure to support new ideas is still a major flaw in the scientific system. New ideas are often rejected for lack of validation of the very idea the investigator wishes to explore. Those

in academic power continue to suppress the new. Yet the observations of Semmelweiss and others promoted the discovery of bacteria by Pasteur and the concept of antisepsis by Lister. All were in part made possible by the 17th century fervor for anatomical studies, the age of the scientific method, the discovery of the microscope and bacterial culture. Similarly, in the 21st century, new ideas that are worthwhile often break through the prejudices and judgment of "peers."

It is Claude Bernard (1813–1878) who really played a major role in development of laboratory methods for the advancement of clinical medicine and hence the advancements that would occur in wound healing in general and the diabetic wounds in particular. "I consider the hospital the antechamber of medicine, it is the first place where the physician makes his observations. But the laboratory is the temple of the science of medicine." Such pronouncement was justified in his day as the practice of medicine had no scientific basis beyond observation. In contrast, Bernard's laboratory findings would lead to scientific facts, which would alter patient care. This philosophy would change drastically in the 20th century when it became obvious that work in animals and cell culture could not supplant the data, which can be derived from human studies.

The late 19th to mid-20th century saw the advent of antibiotics, which has had both positive and negative effects on wound care; mainly, the effects have been positive. Perhaps one of the most interesting observations of discovery in this area again is the fortuitous observation. Yes, Fleming discovered penicillin but as an annoying mold which was hampering his studies of bacteria. It was his associates Chain and Florey who recognized that they should be studying the mold rather than the bacteria and hence penicillin. One must learn from these lessons. Keen and simple observation can change the course of medical history for the better. Failure to look objectively at new ideas can cripple the growth and development of health-related science.

THE EVOLUTION OF WOUND HEALING STUDY

In the 1940s wound healing studies evolved in cell culture, animal models and eventually in man. Alexis Carrel was really the father of modern day wound healing studies for in the first part of the 20th century. He grew fibroblasts in culture, studied wound contraction in World War I combat injuries, and did the first microsurgery (for which he was awarded the Nobel Prize). By the end of War II, many exposed to the devastating injuries of this struggle were stimulated to study wound healing on a more formal basis. These included John Schilling at the University of Oklahoma who created a stainless steel wire mesh chamber, which he implanted subcutaneously in rats. Schilling then measured histological and biochemical events which occurred over time in the chambers. Moreover, the chambers could be injected with various materials to see the effects of these materials on the healing process. About the same time, Egbert Dumphy, at Harvard, started a series of experiments in various animals and humans examining a number of factors which might effect healing including nutrition, oxygen, shock, and so on. Stan Levinson started his medial career in Boston where he witnessed the care of burn victims after the Cocoanut Grove Fire. This early experience led him to his career in burns, wounds, shock, and metabolism. These two surgical leaders published the first texts and symposium on the subject

and either trained or inspired such future leaders in wound healing research such as Tom Hunt who trained with Dumphy and picked up on the Schilling chamber. In parallel, were those spawned from a more traditional academic investigative career. For example, Jerry Gross graduated from Harvard Medical School and went straight into research of developmental biology and tissue repair. Gross actually discovered Gross collaborated with his surgical colleague, Hermes Grillo. Therefore, the basic data of Gross led to Grillo's classic work on the biology of tracheal scarring and contraction. These laboratory experiences led Grillo to the operating room armed with the basic biological principles of healing he had learned working with Gross. In the operating room, he was then able to develop biologically based operations, which were of major importance in the restoring the lives of those with congenital and acquired tracheal injuries.

Working in relative isolation in Chapel Hill North Carolina, a young Erle E. Peacock Jr., stimulated by those mentioned earlier and knowing that collagen was the predominant protein in tissue matrix, performed wound healing experiments involving wound contraction and prevention of scarring using collagen crosslink inhibitors. Like Dumphy, Schilling, and Gross, he mentored many of today's leaders in the wound-healing field.

All of these advances took more than inquisitive ambitious minds. Since the 1970s there has been a logarithmic growth in the laboratory tools available to seek answers to the problems of wound healing pathogenesis in general and diabetic wounds in particular. Wound healing researchers have taken advantage of each new "laboratory toy" which has come along to discover how the "toy" could be used to unlock a wound healing problem crying for solution. Tissue culture, electron microscopy, protein analysis, Western blot, Northern blot, PCR, and now gene array. The list of tools seems endless and increases daily.

Perhaps the greatest discovery for all was the defining structure and means for analysis of DNA and RNA. Without Rosalind Franklin, Watson and Crick, Linus Pauling, and a whole host of scientists of the day, these phenomena and spin off analytical methods would not be available to us. Technology has led to our ability to identify rapidly protein structure, map genes, and characterize materials with great speed accuracy. The explosion of new biological information for those interested in correcting wound-healing abnormalities is dramatic and great strides in our knowledge and therapies is predictable in the near future.

One cannot forget the humanistic areas of science, which has helped in wound care. The pharmacological treatment of depression, education of patients, and caregivers are all part of the advancing science of wound healing. One of the greatest needs along these lines is the education of caregivers, which remains appallingly poor. Perhaps the most important "science of education" to be explored is how to get new valid information to caregivers and see that they learn to separate scientific fact from marketing propaganda.

MAJOR STEPS IN OUR UNDERSTANDING OF WOUND HEALING PROCESS (GROWTH FACTORS, MMPS, AND SO ON)

To treat a clinical wound today without having a basic understanding of the biological principles of wound repair is like trying to sail across the ocean without a compass. (Some of the newer tools being developed will add the equivalent of GPS to the

armamentarium of the clinician.) Several classical wound-healing texts will provide the basics of repair (…) along with Chapter 4 in this text.

WOUND HEALING TODAY: HOW MUCH OF ART AND HOW MUCH OF SCIENCE

In the 45 years that this author has had a focused interest in the biology of wound healing and wound care, there have been few changes in care that make a difference. However, there has been a great deal of exciting science, which has defined some of the basic pathophysiology of chronic wounds. Now it is a matter of increasing the scientific base and translation into clinical care. The science is described in the Chapter by Davison. Moreover, there is a great deal of new science, which relates directly or indirectly to wound healing which increases daily. Many of these advances have been resulting from Federal Government support via the National Institutes of Health (NIH). Unfortunately, most industrial support for wound healing research has been with specific product orientation. However, there are a few significant exceptions to this as some responsible manufacturers have given funds for basic wound healing research.

Perhaps the most interesting phenomena I have observed of wound care product manufacturers is the discovery that wound care is a market worth billions of dollars. Therefore, over the past 25 years, there has been a tremendous drive to dazzle the wound care consumers with virtually thousands of new products each claiming to have an important role in wound management. They have been able to convince third party payers and the federal government that their products should be on the market without much evidence to support their claims. They are driven by profit and not by scientific, clinical truths. They have found spokesmen for their products among "brand name" wound healing nurses and physicians who have sold their endorsements of these therapies for a price rather than take a real objective view of the product. There are some nurses and doctors who have totally lost touch with patient care who market themselves as wound healing experts and travel around the country teaching "wound healing" and often endorsing products of questionable merits. They have created a self-serving business for themselves. Clearly many of the manufacturers and their health care advocates have abused the taxpayer. They have been allowed by the government to add their oft times expensive products of questionable clinical value to the armamentarium used daily for wound care. Moreover, as large populations of wound care givers are nurses, they have fallen for the pseudoscience often offered up by the marketing forces of industry. They are indeed successful and those who actually use the products are won over by marketing rather than scientific data. Unfortunately, the same is true for a number of treating physicians!! Somehow, a strong ethical branch of the wound care industry must ban together with an untainted group of true wound healing experts to develop products, which will actually accelerate the healing of chronic wounds and control the healing aberrations of fibrosis. A leading driver for such reform will come from the federal agencies, which control health care costs and are beginning to look at wound care costs in particular.

AN OUTLOOK OF THE FUTURE

Several events will improve wound care in the next few decades. They can be divided into scientific and care related.

Scientific

1. *Proteases:* why are wounds stuck in an early inflammatory phase and making excessive proteases. Although attaching the protease issue is relevant, it is only the tip of the iceberg. The protease issue looms big. For example, sections in this text will focus on angiogenesis, yet a key to effective angiogenesis will be protease control so angiogenic factors are not destroyed. One possible form of new therapy would be enhancement of endogenous antiproteases. Can one develop gene therapy to enhance the activity of antiproteases and thereby enhance healing? Another would be better understanding and control of free radical production by polymorphonuclear leukocytes (PMNs) as free radicals stimulate inflammation and hence proteases. What are the role of nitric oxide and especially the role of inducible nitric oxide synthase (iNOS) in the induction of inflammation?
2. *Gene Therapy:* we are still wandering in this area and the "scientific tricks," although interesting, are flawed when it comes to clinical application and the health care expenses associated with it. Yet, I expect that we will see cost-effective gene therapy in the future—it will not be soon. Much has been made of stimulating growth factor production with gene therapy. It would seem more appropriate to direct attention at gene therapy to inhibit proteases as growth factors will never be effective in the presence of high levels of proteases.
3. Modulation of temperature to control pressure necrosis leads to cell death and ulcer formation in the patient with diabetes. Cooling as well as pressure relief will be important in the management of diabetic foot wounds. Cooling to prevent the inflammatory changes with pressure and the flow–reflow phenomena may provide a very simple form of low-cost improvement in our prevention of diabetic wounds and pressure sores. After all, pressure is a major cause of both chronic wounds.
4. New drugs to treat diabetes itself: the better one can keep blood sugar in a normal range, the less glycosylation there is of all sorts of tissues in the body; hence the fewer diabetic complications.

Care-Related Issues

1. Industry must "clean house" and listen to the science rather than the marketing genius who will simply push product rather than the scientific basis of the product.
2. Education: many of the "courses" on wound healing simply propagate bad ideas and practice. There are even national meetings, which are contaminated by bad data given by bad speakers.
3. The concept of wound healing centers is excellent, but often the execution is lacking. There must be more formal education for the health care gives in these centers and frequent reviews and updates.
4. We live in an era in which computerized communication is superb, yet we in wound healing have not taken advantage of this for the benefit or our patients. Google and PubMed are a big help for those willing to dig out data. However, the busy practitioner needs to be fed information in a simple and easily accessed fashion. More can be done
5. The federal government should be more involved in evaluation of products for their scientific merit and having some control over what is and what is not paid for by government agencies.
6. Every wound is attached to the patient and the patient must be treated emotionally as well as physically. Every wound is associated with an underlying pathological process and all of these phenomena must be examined in great detail. How often I am referred a wound rather than being referred a patient. How often I discover that the patient has not had an adequate evaluation. Once the emotional aspects are clear and the patient becomes part of the wound care team and once the underlying disease is properly treated, it is amazing how well the patient will do and the wound will heal without expensive or esoteric therapies.
7. Finally, I urge basic scientists, clinicians and even government regulators to get involved in wound healing. The problem is enormous worldwide and needs major attention. The incidence of diabetes and morbidity and mortality from the diabetic wound continues out of

control. Not enough attention is being paid to the problem and all must fight this dreaded disease and its complications.

SUGGESTED READING

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